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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/464,795
Filing Date: December 16, 1999
Appellant(s): ZHANG ET AL.

Dahna S. Pasternak
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 7, 2006 appealing from the Office action mailed February 8, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Boyd et al. (1993) Molecular biology of transgenic animals. Journal of Animal Science 71(Suppl. 3): 1-9.

Cameron, ER (1997) Recent advances in transgenic technology. Molecular Biotechnology 7: 253-265.

Cui et al. (1994) Reporter genes in transgenic mice. Transgenic Research 3: 182-194.

Hammer et al. (1990) Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2m: An animal model of HLA-B27-associated human disorders. Cell (63): 1099-1112.

Mullins et al. (1993) Transgenesis in nonmurine species. Hypertension 22: 630-633.

Shibahara et al. (1989) Structural organization of the human heme oxygenase gene and the function of its promoter. Eur. J. Biochem. 179: 557-563, abstract only.

Wood, PA (2000) Phenotype assessment: Are you missing something? Comparative Medicine 50(1): 12-15.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Utility

Claims 38, 40, 41, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

A careful reading of the specification reveals only one asserted utility for transgenic mice comprising multiple expression cassettes as recited in the claims. The asserted utility is to use the mice to identify agents that induce or repress expression of the reporter gene (i.e., the "light generating polypeptide") with the express purpose of determining how various agents present in the environment affect native gene expression in humans and other animals and, more specifically, how the agents affect the particular genetic control elements present in the reporter constructs. However, the instant claims recite the use of a "promoter derived from a …stress-inducible gene" operably linked to sequences encoding a light generating polypeptide. The claims do not recite the presence of a stress-inducible control element. Thus, the term "promoter derived from a …stress-inducible gene" covers minimal promoters, truncated promoters, and promoters lacking their endogenous enhancers and inducible elements. When transgene constructs are made, such that a promoter is operably linked to a protein

coding sequence, the promoter must necessarily be **truncated** to insert it into the expression vector. As such, depending on where the truncation is made, variable portions of important regulatory elements may either be included or excluded from the construct. There is nothing in the claims that requires the inclusion of any particular regulatory elements beyond a basal or minimal promoter structure. Furthermore, there is no specific guidance on which portions should be included or which portions can be excluded (and still produce a relevant experimental system). Thus, the relevance of the experimental system is highly dependent on the retention of **all** the relevant native regulatory regions that modulate promoter function. In the present claims, none are required. Thus, the instant claims cover a great variety of transgenic mice that **cannot be used for the asserted utility** because they do not contain inducible genetic elements in combination with the "promoter derived from a …stress-inducible gene" recited in the claims. Such mice would not be useful in assaying agents to determine how they affect native gene expression. As a further issue, the claims cover a wide variety of transgenic mice that have combinations of control elements that are in no way representative of the native expression of the genes from which they are derived because the combinations are artificial. As discussed below, the specification explicitly contemplates using a large variety of artificial contructs in the transgenic mouse. However, the skilled artisan would not be able to correlate the result obtained in carrying out a screening assay as defined, for example, in Claim 40, to the function of the pertinent control elements in their native context. The specification does not assert a utility for the use of constructs that have combinations of control elements that do not represent their native context.

With regard to other control elements that may or may not be present in combination with the promoter, the specification discloses the following at page 33:

> "The control element (e.g., a promoter) may be from the same species as the transgenic animal (e.g., mouse promoter used in construct to make transgenic mouse), from a different species (e.g., human promoter used in construct to make transgenic mouse), **or a mixed control element (e.g., some control elements from a mouse promoter combined with some control elements of a human promoter)**."
> Specification at page 33, lines 26-30, emphasis added.

The specification further discloses, at pages 11-12, that control elements may be as follows:

> "Typical control elements or expression control elements or regulatory sequences, include, but are not limited to transcription promoters, transcription enhancer elements, transcription termination signals, polyadenylation sequences (located 3' to the translation stop codon), sequences for optimization of initiation of translation (located 5' to the coding sequence), translation enhancing sequences, and translation termination sequences. Transcription promoters can include inducible promoters (where expression of a polynucleotide sequence operably linked to the promoter is induced by an analyte, cofactor, regulatory protein, etc.), repressible promoters (where expression of a polynucleotide sequence operably linked to the promoter is induced [sic] by an analyte, cofactor, regulatory protein, etc.), and constitutive promoters.
>
> Expression enhancing sequences typically refer to control elements that improve transcription or translation of a polynucleotide relative to the expression level in the absence of such control elements (for example, promoters, promoter enhancers, enhancer elements, and translational enhancers (e.g., Shine and Delagarno [sic] sequences))."
> Specification at pages 11-12.

Thus, although the specification contemplates using various control elements in combination with a "promoter derived from a … stress-inducible gene" it does not assert any utility for **artificial** contructs, where unrelated control elements are combined with the promoter, as opposed to constructs that retain all the relevant **native** regulatory regions that modulate promoter function.

MPEP 2107.02(I) states that

> Where an applicant has established utility for a species that falls within an identified genus of compounds, and presents a generic claim covering the genus, as a general matter, that claim should be treated as being sufficient under 35 U.S.C. 101. Only where it can be established that other species clearly encompassed by the claim do not have utility should a rejection be imposed on the generic claim. In such cases, the applicant should be encouraged to amend the generic claim so as to exclude the species that lack utility.

The asserted utility, as discussed above, is not applicable to the vast majority of transgenic mice covered by the claims. Thus, an asserted utility is lacking for a very large scope of the claims. Following the guidance of the MPEP "the applicant should be encouraged to amend the generic claim so as to exclude the species that lack utility" (MPEP 2107.02(I)). However, in the instant case, the Examiner finds no language within the specification that points specifically to the genus of constructs that would

produce transgenic mice **useful for the asserted utility**, which is to provide an assay system to determine the effect of various agents on the promoter and its control elements in a manner that correlates to the native function of the element in its native context. The specification provides no assertion of utility whatsoever for artificial constructs that have no bearing on native gene function.

The specification fails to provide a utility that is generic to the entire scope of the claim. While the specification could assert separate utilities for the different embodiments covered by the claims, here it does not. Instead, a very large number of embodiments have no utility at all.

The claims are directed to transgenic mice comprising two or more expression cassettes and methods of using those mice. First and foremost, it is again noted that the claims do not require the presence of a single stress-inducible control element in the mice. On the contrary, the claims recite the use of a "promoter derived from a … stress-inducible gene." Thus, the particular promoter included in the expression cassette need not include any **stress-inducible** elements at all. Further, the nature and number of derivative processes used to select a "promoter derived from a … stress-inducible gene" are not defined. Any portion of the promoter may be included or excluded. Second, even if the claims did recite the presence of a stress-inducible control element, the context in which the control element resides (e.g., combined with other unrelated control elements and/or inserted into the genome within a site that is influenced by the endogenous control elements surrounding the expression cassettes) is in no way required to correlate with the native context of the stress-inducible genetic control elements. In such cases, the function of the artificial construct would in no way pertain to the function of the promoter and its regulatory elements in their native context. As discussed in more detail below, when dealing with transgenic mice, the genomic site of insertion of a transgene greatly influences the expression of the transgene. While the *ex vivo* genetic context of the transgene construct may be controlled by the practitioner in designing the transgene construct, once the transgene is inserted into the mouse genome,

the genetic context changes. Upon insertion into the genome, the transgene construct is surrounded by endogenous genetic elements, including enhancers which can exert their influence over long distances.

The asserted utility of using the mouse or method to study gene expression applies only to those experimental systems that recapitulate **native** gene expression, and the claims are not directed to or limited to such constructs/experimental systems. The instant claims cover a great variety of transgenic mice, harboring a great variety of transgene constructs that are unrelated to the asserted utility. The claims cover the use of constructs that have no bearing on native gene expression. The **claimed** invention does not require the presence of a "stress-inducible promoter." The mere presence of a "promoter derived from a first stress-inducible gene" and another "promoter derived from a second stress-inducible gene" would be sufficient to meet the claim limitations (Claim 38) and would be induced by **nothing**. Clearly, there is **no** specific and substantial utility for transgenic mice bearing such constructs, because **the asserted utility does not pertain to such mice.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 38, 40, 41, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advance in the prior Office Actions of 2/1/01, 9/13/01, 8/27/02, 5/21/03, 10/5/04, 5/17/05, 10/31/05, 2/8/06, and 4/28/06, as summarized here, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description guidelines state, "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics."

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, at a minimum the transgene constructs and site of integration, whether random or targeted (i.e., site-specific) should be sufficiently described, such that the phenotypic consequences of altering the genotype have been described. In this case, the specification provides the general methodology for making transgenic animals (see page 65, lines 2-7 and pages 65-68 of the specification), but does not describe any working example for producing a transgenic mouse as claimed and does not describe the expression characteristics of a transgenic mouse encompassed by the claimed invention. It is further noted that considering the fact that the art of making transgenic animals is highly unpredictable, the phenotypes and characteristics of the transgenic mice encompassed by the invention are not predictable. Additionally, due to the unpredictability of the site of integration of the transgene, when random integration methods are used, the final genetic context of the expression cassettes is not described. The specification does not identify and describe a site within the mouse genome that would be insulated from the surrounding endogenous genetic elements in the mouse genome. When methods that result in random integration of the transgene are used, the surrounding endogenous genetic elements are unknown and undefined.

The claims are directed to mice comprising transgene constructs that comprise a wide variety of promoters (derived from a stress-inducible gene), with no description of which portions of the promoter

are to be included. The promoter is an essential element of the claimed invention and neither the specification nor the prior art sufficiently describes the full array of promoters covered by the claims. Not surprisingly, different promoters from stress-inducible genes have been characterized to different degrees in the prior art (see the abstract in Shibahara et al. Eur J Bichem 179:557-563, 1989 which provides a limited description of a human heme oxygenase promoter). The skilled artisan would be required to rely on the teachings of the prior art for extensive teachings relating to the full array of promoters that fall within the scope of the claim. However, the prior art does not provide a description of the necessary promoter portions for the very large genus of stress-inducible genes covered by the claims.

The portions of the "promoter derived from a … stress-inducible gene" that should be used in the expression cassettes are not described. The specification does not describe the promoter portion to be used in the expression cassette as including any specific portion of the upstream regulatory region, such as 10 kb, 1 kb, 500 base pairs, 100 base pairs, etc. Given its broadest reasonable interpretation, the term "promoter derived from a … stress-inducible gene" covers minimal promoters, truncated promoters, and promoters lacking their endogenous inducible elements. Since stress-inducible elements are not required to be present in the expression cassettes, it is unclear how the asserted utility would be achieved because such a construct would be induced by **nothing.** Thus, the presence of a "promoter" as broadly defined, would not represent native gene expression.

The disclosure makes it clear that the desired goal of the invention is to prepare contructs relevant to native gene expression in an *in vivo* context and then to use those constructs to observe the effects of various treatments or agents on the promoter activity, but the specification has not described those constructs that will provide for native gene expression. The claims encompass mice comprising transgene constructs that comprise a wide variety of regulatory elements from stress-inducible genes, as discussed above (ranging from a minimal promoter to a 10kb upstream region or larger), but there is insufficient description of constructs that provide for native gene expression.

The rejection of recorded is grounded in the failure of the specification to describe those constructs that will provide for native gene expression and thereby be representative of **native gene expression**, such that the effect of an analyte on the construct will be representative of the effect of the analyte on the promoter (and its elements) in its native context. The specification makes it clear that the desired goal of the invention is to prepare constructs **relevant to native gene expression** in an *in vivo* context and then to use those constructs to observe the effects of various treatments or agents on the promoter activity, but the specification has not described those constructs that will provide for **native gene expression** when integrated into a mouse genome.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of incorporating an exogenous gene by random integration can not be predicted. Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted,

> "Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

The art teaches that phenotype of a transgenic mouse cannot be predicted. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

> "The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes and more. It is, however, common to hear that surprisingly a given model has 'no phenotype'."

In the instant application, it is not clear what would have been the result of incorporating two or more expression constructs in the genome of a mouse, given the great variety of transgene constructs (i.e., expression cassettes) encompassed by the claims.

With the limited information disclosed in the specification, an artisan would not have been able to predict the phenotypic response resulting from the various genetic manipulations covered by the claims. Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the very large number of embodiments encompassed by the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed the invention.

Enablement

Claims 38, 40, 41, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in the prior Office Actions of 2/1/01, 9/13/01, 8/27/02, 5/21/03, 10/5/04, 5/17/05, 10/31/05, 2/8/06, and 4/28/06, as summarized here, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the specification provides sufficient guidance to make and use the claimed invention, and if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of

direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

MPEP 2164.03 states that:

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling."

The claimed invention encompasses transgenic mice that comprise a panel of expression cassettes wherein said panel comprises 2 or more expression cassettes which in turn comprise a promoter from a stress-inducible gene operably linked to a light generating polypeptide. Different expression cassettes in a particular transgenic animal may comprise control elements of different stress-inducible genes and different light generating polypeptides. The claimed invention also encompasses methods of determining the effect of an analyte on gene expression mediated by the claim-designated promoter by administering the analyte to the transgenic mouse and determining light generation from the light generating polypeptide in the transgenic mouse under appropriate conditions.

The specification fails to provide an enabling disclosure for the claimed transgenic mouse and methods of using the mouse because the specification does not provide sufficient guidance, evidence, and working examples to produce transgenic mice useful for the asserted utility, which is to analyze the effect of various compounds on inducible elements that may not even be present in the claimed transgenic mice.

The current state of the art demonstrates that genetic control elements function differently in different species. Investigators observed 5-70 fold lower yields of a recombinant protein in transgenic mice when they used a construct designed for expression in sheep (see lines 1-12 in 4th para of col 1 on page 632 in Mullins et al. (Mullins JJ et al. Hypertension 22:630-633,1993)). The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors.

In a more recent assessment of transgenic technology, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

As a further example of the differences in the behavior of genetic control elements across species, Hammer et al (Hammer RE et al. Cell 63:1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic responses. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would

have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been taken to address this issue?

Introduction of foreign DNA into a fertilized oocyte by pronuclear microinjection results in random integration of the exogenous DNA into host chromosomal DNA which in turn can have major consequences on the expression of the transgene. Thus, the expression of a transgene in a mouse can be highly variable and unpredictable. As noted above by Cameron et al even making a transgenic mouse with a certain phenotype is not predictable because it is unpredictable whether an artisan can produce a transgenic mouse of same phenotype a second time using the same expression construct. Cui et al. (1994, Transgenic Research 3:182-194) reviewing the state of the art of reporter genes in transgenic mice noted that when a lacZ construct was introduced in ES cells by electroporation and the resultant ES cells were injected into blastocysts and whole embryos were tested for lacZ expression, each strain manifested a unique pattern of transgene expression indicating that the expression of the transgene is dependent on the site of integration (see last paragraph in column 1 on page 184). It is noted that in the instant case the transgenic mice comprise more than one expression construct, and when the expression of one construct is not predictable, it is not clear how the expression of multiple constructs can be predicted. Yet another unpredictability of making transgenic mice with reporter genes has been the unpredictability whether the reporter gene would be expressed post-natally, even if the reporter gene was expressed at the embryonic stage. Again Cui et al noted that the same promoter that expressed reporter gene lacZ in embryo did not direct expression in adult (see column 2 on page 186). While Cui et al used the example of lacZ, given the teachings of the prior art and limited teachings of the specification, it is likewise unpredictable whether the reporter genes of the instantly claimed invention would produce varying levels of expression in the embryos and adult animals.

Additionally, in the claimed methods (claims 40, 41, 45, and 46), first an analyte has to be administered to the transgenic mouse which has to reach the promoter of the transgene in the nucleus of a cell after it has entered a cell via a receptor or any other method and an analyte may affect more than one stress gene and the extent of effect may not be distinguishable from each other. The specification at pages 35-41 has disclosed an extensive list of gene whose expression is altered under stress and therefore, their promoters may be used in the expression constructs in any combination of at least two promoters. However, the specification does not provide any guidance as to whether the activity of all these elements would have been affected by an analyte *in vivo* when the promoter is inserted in the genome not at its natural site. Additionally, the specification does not provide any guidance as to whether these promoters would have behaved in directing reporter gene expression as they regulate the expression of their natural coding sequences. After the luciferase enzyme is produced in a cell it has to interact with the substrate to emit light, which would then be captured. Additionally, the claimed invention recites more than one light producing polypeptide in the transgenic mouse. A multitude of all these factors (one or more) will affect the final detection of bioluminescence and the specification does not provide any guidance as to whether the results obtained in the method would be a true representation of the changes in the promoter activity present in the transgenic mouse. The instantly claimed method is intended to differentiate between the expression level of multiple promoters in the absence or presence of an analyte that not only affects the activity of said promoters but may affect the metabolism of the transgenic mouse itself. It is reiterated that the specification does not disclose a working example of the transgenic mouse or a method of using said transgenic mouse.

The particular promoter regions used and the method of inserting the expression cassettes into the genome of the mouse are critical to the operability of the claimed invention. The expression (or lack thereof) of the reporter gene upon administration of an analyte depends on a number of parameters, including the particular promoter region used in the expression cassette, the particular combination of

expression cassettes within the mouse, the integration site within the genome, the effect of endogenous control elements surrounding the integration site of each cassette, and the particular array of light generating polypeptides used in the various expression constructs introduced into the mouse, all of which are ill-defined by both the specification and the claim limitations.

The level of expression of a reporter gene will depend on the particular combination of elements used to drive and regulate its expression, the "completeness" of the promoter element outside of its native context, and the authenticity of the new context within the genome into which the expression cassette is inserted. The endogenous control elements surrounding the transgene insertion site will affect expression of the reporter cassette, to an unpredictable extent. Preparing a transgene construct necessarily requires the truncation of a gene's upstream promoter elements and subsequent operable linkage of the truncated promoter element to the reporter gene. Ultimately, the expression cassette must be inserted into the mouse genome either randomly or by targeted integration to produce a mouse that expresses the reporter gene in a manner that is representative of and predictive of the activity of the control elements in their native context. The instant specification provides little to no guidance for achieving reporter gene expression that is relevant to native gene expression in a living animal, particularly given the broad scope of the various promoter regions covered by the claims and the artificial combinations that are contemplated and covered.

The specification contemplates producing artificial gene regulatory regions by combining control elements from various sources (e.g., human, mouse) with no guidance on how such constructs would be useful in elucidating the function of control elements in their native context. Thus, it would be up to the skilled artisan to determine, based on extensive experimentation, what guidance in the specification is useful guidance and what is not for any given embodiment. Furthermore, in view of the very broad scope of constructs that can be used in the transgenic mice, considerable guidance would be required to correlate the result obtained in the analyte screening assay with the effect of the analyte on native gene

expression. However, the specification does not offer such guidance. Thus, the skilled artisan would not be able to obtain a useful result that is relevant to the promoter region being studied.

The particular promoter portions (and upstream portions of the regulatory region of the gene) used and the method of inserting the expression cassettes into the genome of the mouse are critical to the operability of the claimed invention. The specification teaches that only those promoter portions that recapitulate native gene expression have utility in the claimed invention, but the specification fails to enable the identification of such promoter portions such that the native context is retained when the promoter is truncated and inserted into an expression cassette, which is then inserted into the genome of a mouse (in a new genetic context).

In summary, the state of the art of transgenic mice is highly unpredictable and unless a transgenic mouse has been produced, one cannot predict the expression characteristics of a transgenic mouse comprising a given expression construct. It is emphasized that USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. Therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

It is therefore concluded that the specification fails to provide specific guidance as to how an artisan would have dealt with the art-recognized limitations inherent to transgenic mice and therefore, the production of transgenic mice as claimed and their use in the recited methods would have necessitated undue experimentation on the part of one skilled in the art.

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.")

Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

(10) Response to Argument

At page 6 of the brief, Appellants assert that "the evidence of record establishes that the as-filed specification sets forth patentable utilities." It is unclear what "evidence of record" Appellants are referring to because the brief does not contain any evidence relied upon in the Evidence Appendix.

At page 6 of the brief, Appellants further assert that transgenic mice containing reporter constructs recapitulate native gene expression. Appellants state that, at the time of filing, reporter constructs containing a promoter of a gene of interest operably linked to a reporter sequence were the preferred way of recapitulating native gene expression both *in vivo* and *in vitro*. Appellants refer to the specification at page 3 for describing the use of reporter constructs to recapitulate native gene expression. The cited section refers to the use of tissue-specific promoters in transgenic mice and the study of the regulation of insulin-responsive glucose transporter GLUT4 and ApoA-I genes in transgenic mice. First, although the quote contained in the brief omits the citations for these examples, the Examiner has referred to the section of the specification and finds that the literature references cited are not of record in this case. Second, none of these examples in the literature pertain to double, triple, or other multi-transgenic mice. Each mouse model contained only one transgene and it was the expression of the protein that was the focus of the study and critical to producing the phenotype observed (i.e., a disease phenotype). Third, the regulatory regions included in those transgenes were not the focus of the study, and therefore it cannot be said that the regulatory regions used provided for **native** gene expression for the genes being studied. In fact, most transgenic mouse studies that involve expression of an exogenous gene, rely on

overexpression of the gene to produce a desired phenotype. Fourth, since the literature references cited in the relevant section of the specification are not of record, the specifics involved in constructing those transgenic mice are not provided.

At page 7 of the brief, Appellants assert that "[t]he actual 'asserted utility' is well-established, substantial and specific." Appellants assert that the MPEP states that a utility rejection should not be imposed when the invention has a well-established utility or when a specific and substantial utility has been asserted. However, as noted above, the MPEP explicitly provides that when the claim clearly encompasses species that do not have utility, a rejection should be imposed on the generic claim and the applicant should be encouraged to amend the generic claim so as to exclude the species that lack utility.

MPEP 2107.02(I) states that

> Where an applicant has established utility for a species that falls within an identified genus of compounds, and presents a generic claim covering the genus, as a general matter, that claim should be treated as being sufficient under 35 U.S.C. 101. Only where it can be established that other species clearly encompassed by the claim do not have utility should a rejection be imposed on the generic claim. In such cases, the applicant should be encouraged to amend the generic claim so as to exclude the species that lack utility.

Appellants have not addressed this issue.

At page 8 of the brief, Appellants conclude that the "evidence of record" demonstrates that reporter constructs recapitulate native gene expression by virtue of the promoter selected. Again, it is unclear what "evidence of record" Appellants are relying on because there is nothing in the Evidence Appendix of this brief. There is no evidence that promoter portions as claimed would recapitulate native gene expression.

At pages 8-9 of the brief, Appellants assert that there is ample description in the specification, in view of what was well known in the art, and that the specification "need not teach, and preferably omits, what is well known in the art," citing *Spectra-Physics, Inc. v. Coherent, Inc.* Appellants again refer to a section of the specification that cites literature references that are not of record. Thus, the details of those

references are not available for all that they teach and are not under scrutiny here. Nevertheless, suffice it to say, that the judicious selection of regulatory regions of a gene cannot occur absent a description of those elements that are necessary and sufficient to drive expression of a reporter gene in a manner that is representative of the native expression of the gene from which the regulatory elements were obtained. Here, with the objective being to test the inducibility/repressibility of the stress-inducible gene of interest, more than just a minimal promoter portion of the gene would be required. However, the instant specification does not describe those regulatory regions that are critical, where they are located, or their upstream boundaries. Even if some critical regulatory regions are described for a few genes, those critical regulatory regions are not required to be included in the expression cassettes, given the present claim language.

At page 11 of the brief, Appellants assert that reporter molecules as claimed were known to predict native gene expression, both *in vivo* and *in vitro*. No support is offered for this assertion. The claimed invention requires the generation of transgenic mice having promoters that regulate expression of the light generating proteins in a manner that is **predictive** of native gene expression (the only asserted utility for the claimed transgenic mouse). The particular promoter portions (and upstream portions of the regulatory region of the gene) used and the method of inserting the expression cassettes into the genome of the mouse are critical to the operability of the claimed invention. The specification teaches that only those promoter portions that recapitulate native gene expression have utility in the claimed invention, but the specification fails to enable the identification of such promoter portions such that the native context is retained when the promoter is truncated and inserted into an expression cassette, which is then inserted into the genome of a mouse (in a new genetic context).

At page 12 of the brief, Appellants state that the allegation that the specification is required to enable identification of promoter portions is unsupported. Appellants assert that the promoter portions were well known at the time of filing and that the specification describes these promoters and portions

thereof (including CREs). Appellants cite a section of the specification at page 33 that refers to a common response element (CRE). However, the claim-designated expression cassettes are not required to contain one of these response elements, but instead are only required to have a "promoter derived from a … stress-inducible gene." Whether or not specific response elements are known for a particular stress-inducible gene depends on how well characterized the upstream regulatory region of the gene is in the prior art. It is maintained that the instant specification does not provide specific guidance for identifying those portions of the promoter region that are necessary and sufficient to achieve native patterns of gene expression.

At page 13 of the brief, Appellants assert that the claim term "operably linked" is defined in the specification such that "the promoter of the reporter construct is required to perform its usual (native), function, i.e., recapitulate native gene expression." Appellants provide a quote from page 12 of the specification which notes that when a given promoter is operably linked to a coding sequence, it is capable of effecting the expression of the coding sequence when the proper enzymes are present. This does not in any way imply or require the presence of other regulatory elements that modulate the function of the promoter. One of skill in the art would readily recognize that a promoter region isolated from the regulatory elements that normally modulate its function, would not provide for a pattern of gene expression that is representative of the native expression of the gene from which it was obtained. Nevertheless, specific guidance for identifying all elements that are necessary and sufficient to provide for a native pattern of gene expression is lacking. The specification is clear that the intention is to create a construct and experimental system that recapitulates **native gene expression**, not gene expression in an artificial context. The specification does not provide specific guidance for creating constructs, within the scope of the claims, that have this utility and the claims are not directed to or limited to such constructs/experimental systems.

At page 13 of the brief, Appellants again refer to the "evidence of record" as establishing that recapitulating native gene expression in a transgenic mouse comprising a single reporter construct including a light generating reporter was known. Again, it is unclear to what "evidence of record" Appellants are referring. It can only be assumed that Appellants are referring to the specification itself. As noted in the rejection of record, however, the instant specification discloses no working examples and given the unpredictability in the transgenic art, the broad scope of the claims, the limited guidance of the specification, the lack of any working example, and the quantity of experimentation needed to enable the instant claims across a very broad scope, undue experimentation would have been required for one skilled in the art to make and use the invention as claimed.

Unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those skilled in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, there is no evidence in the specification which supports that the very large number of embodiments encompassed by the claims, including mice that contain artificial constructs that vary considerably from their native arrangement, can be readily obtained without undue experimentation.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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